IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Ian H. FRAZER	)	Confirmation No: 8451
	)	
Application No.: 10/534,130	)	Art Unit: 1633
	)	
Filed: December 30, 2005	)	Examiner: Janet Epps Ford
	)	

For: A METHOD FOR OPTIMISING GENE EXPRESSION USING SYNONYMOUS CODON OPTIMISATION

Declaration under 37 C.F.R. § 1.132 of Professor Ian H. Frazer

I, Ian H. Frazer, declare and say:

1. I am the inventor of the captioned application.

2. A copy of my *Curriculum Vitae* was presented previously with the declaration accompanying the response filed on November 6, 2008 ("the November 6, 2008 declaration").

3. I have reviewed the Office Action dated 6 October, 2009 in which the Examiner asserts that the methodologies and data discussed in the November 6, 2008 declaration were not present in the specification as originally filed. The Examiner further asserts that the ranking of immune response preferences obtained using those methodologies is only applicable to the E7 protein rather than to antigens in general. On these bases the Examiner alleges that the specification does not provide the skilled artisan with sufficient guidance for practicing the full scope of the claimed invention without undue experimentation. I explain below why one skilled in the art readily could have practiced the full scope of the claimed invention without undue experimentation at the time that the captioned application was filed.

4. The constructs described in the November 6, 2008 declaration (the "Series II constructs") are functionally equivalent to those disclosed in the present specification (the "Series I constructs") in that they both permit determination of the influence of different synonymous codons on the immune response in whole organisms against the antigen encoded by the construct.

5. The only difference between the Series I and II constructs is that the

Series II constructs were modified to include a secretory sequence that targets the encoded antigen to the secretory pathway, so as to improve the antibody titers obtained in immunized animals as described, for example, in an article by Rush *et al.* *J. Immunol.* 2002, Nov 1; 169: 4951-4960. A copy of this article is ***attached*** in APPENDIX A.

5. To show that the Series I constructs can be used to obtain similar results as the Series II constructs, I describe below experiments and data generated using an example of the Series I constructs disclosed in the present specification.

6. Specifically, constructs encoding an N-terminal secretory sequence followed by a linker sequence (XXGXGXX, where X is the relevant amino acid for a particular construct and G is glycine) and the E7 protein were made for each of the following amino acids: Asn, Ala, Lys, Arg, Phe, His and Tyr.

7. The constructs were prepared in the pCDNA3 vector (Invitrogen) and were delivered to mice using the Helios Gene Gun System (Biorad). The antibody immune responses in the mice were measured using an ELISA assay. The results obtained were used to generate a ranking of immune response preferences for codons, as shown in APPENDIX B.

8. Comparison of the immune response preferences shown in APPENDIX B with those shown in Appendix C of the November 6, 2008 declaration shows that the ranking of immune response preferences obtained using the Series I constructs described above is entirely consistent with the ranking of immune response preferences obtained using the Series II constructs.

9. Furthermore, the ranking of immune response preferences can be used to modulate the antibody immune response against any antigen of interest, as shown for example in a Example 12 of WO 2009/049350, which discloses that modifying wild-type HPV E7 and HSV gD2 coding sequences to include synonymous codons with higher preferences for conferring an antibody immune response significantly increases antibody titers in immunized animals, as compared to the antibody titers obtained using the wild-type sequences. A copy of WO 2009/049350 is ***attached*** in APPENDIX C.

10. All statements made herein of my knowledge are true and all statements made on information and belief are believed to be true; and further, these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any document or any registration resulting therefrom.

Date: 5th April 2010

Ian Frazer